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RESEARCH ARTICLE

Hippocampal volume indexes neurobiological sensitivity to the effect of pollution burden on telomere length in adolescents

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Abstract

Exposure to environmental pollutants has been associated with cellular aging in children and adolescents. Individuals may vary, however, in their sensitivity or vulnerability to the effects of environmental pollutants. Larger hippocampal volume has emerged as a potential index of increased sensitivity to social contexts. In exploratory analyses (N = 214), we extend work in this area by providing evidence that larger hippocampal volume in early adolescence reflects increased sensitivity to the effect of neighborhood pollution burden on telomere length (standardized β = –0.40, 95% CI[–0.65, –0.15]). In contrast, smaller hippocampal volume appears to buffer this association (standardized β = 0.02). In youth with larger hippocampal volume, pollution burden was indirectly associated with shorter telomere length approximately 2 years later through shorter telomere length at baseline (indirect standardized β = –0.25, 95% CI[–0.40, 0.10]). For these youth, living in high or low pollution-burdened neighborhoods may predispose them to develop shorter or longer telomeres, respectively, later in adolescence.

KEYWORDS
adolescence, biological aging, biological sensitivity to context, pollution, telomeres

1 | INTRODUCTION

Exposure to environmental pollutants and contaminants, such as air pollution, heavy metals, and pesticides, has been associated with increased risk for health problems, from hypertension, to respiratory and cardiovascular disease, to Alzheimer's disease, and depression (Brook et al., 2010; Manczak et al., 2020; Mir et al., 2020; Navas et al., 2007; Reuben et al., 2021). One mechanism that might underlie the association between pollutant exposure and disease is accelerated rates of biological aging, often measured by telomere length (Liu et al., 2021; Martens et al., 2017). Telomeres are protein caps located at the ends of chromosomes that protect the genome and serve as a marker of cellular aging (Blackburn, 2000). Telomere length shortens during cell division that occurs over the course of chronological aging, leading to processes that contribute to cellular senescence, apoptosis, and DNA damage response (e.g., mechanisms for the detection of DNA lesions and promotion of DNA repair) (Ye et al., 2014). Pollution exposure can lead to biological processes such as excessive inflammation and oxidative stress (Kelishadi et al., 2009; Leni et al., 2020) that have been associated with a faster rate of telomere shortening (Houben et al., 2008). Indeed, children and adolescents living in communities with higher levels of pollution and contaminants have been found to have shorter telomere length (Clemente et al., n.d.; Fillman et al., 2016; Lee et al., 2019), suggesting that the adverse effects of pollutants on accelerated biological aging start early in life.

There are likely to be individual differences in sensitivity to the effects of pollution on health and developmental outcomes (Trentacosta & Mulligan, 2020). In humans, much of the work on individual variation has focused on nutritional and psychosocial characteristics as protective or vulnerability factors for adverse consequences of pollution (Trentacosta & Mulligan, 2020). For example, iron rich diets and supplements may decrease lead concentration in blood (Kordas, 2017). Similarly, selenium supplements may help to mitigate health effects related to mercury toxicity (Spiller et al., 2018). In research on psychosocial moderators of the link between pollutant exposure and adverse health outcomes, the associations between air pollution and stress biology in adolescents are stronger in youth who report experiencing more severe mental health difficulties (Miller et al., 2020; Miller et al., 2019). Further, adolescents who experience less parental psychological control have been found to be buffered from the association between drinking water contaminants and elevated depressive symptoms (Manczak et al., 2020), and children exposed to violence have been found to be vulnerable to the effects of air pollution on the development of asthma (Clougherty et al., 2007). Neurobiological factors, including those that are sensitive to early experience such as childhood stress (McEwen, 2012), may also interact with pollutant exposure to affect health (Boyce, 2016). While studies such as these are promising, research to date has not considered individual variability in sensitivity to the effects of pollution on telomere length.

The biological sensitivity to context (and differential susceptibility) and diathesis stress models are two dominant perspectives guiding current research on sensitivity and vulnerability to social environments (Belsky, 2016; Boyce, 2016; Colodro-Conde et al., 2018). The biological sensitivity to context model posits that neurobiological markers indicate plasticity or malleability that predisposes individuals to develop, on one hand, better outcomes in supportive, advantaged (i.e., resource rich) environments, but on the other hand, more problems in adverse environments (Boyce, 2016). Conversely, the diathesis stress model predicts that although some individuals are more vulnerable to the negative effects of adversity, they do not fare better than do other individuals in advantaged environments (Belsky & Pluess, 2009; Monroe & Simons et al., 1991). Researchers interested in these models have tested neurobiological functioning in adolescents as a possible moderator of the

association between wellbeing and a number of social environmental factors, including parenting (Deane et al., 2020), peer stress (Eisenlohr-Moul et al., 2018), and stress and family adversity related to the COVID-19 pandemic (Miller, Chahal, et al., 2021). In the present study we extend this literature by drawing on these theoretical models to consider sensitivity versus vulnerability to a specific form of adversity in the physical environment – pollution burden. Environmental pollutants and social adversity have been linked to similar health outcomes in children and adolescents, including more severe internalizing problems (LeMoult et al., 2020; Yolton et al., 2019) and accelerated biological aging (Colich et al., 2020; Lee et al., 2019). In addition, pollution and social adversities affect health through many of the same biological processes, such as inflammation and allostatic load (McEwen & Tucker, 2011; Olvera Alvarez et al., 2018). Given that social adversity and pollution share pathways to similar health outcomes, some processes may regulate sensitivity or vulnerability to the adverse effects of both types of exposure.

The brain is the central organ in perceiving and responding to environmental input (McEwen, 2012). Therefore, a growing body of research is examining brain-based measures of neurobiological sensitivity and vulnerability to social adversities (Guyer, 2020; Schriber & Guyer, 2016; Turpyn et al., 2021). Hippocampal volume is emerging from this literature as a potential neurobiological marker of sensitivity to context. For example, compared to adolescent girls with smaller hippocampal volume, girls with larger hippocampal volume have been found to be more sensitive to effects of maternal aggression on changes in depressive symptoms over time (Whittle et al., 2011), and further, to experience the most and least severe depressive symptoms in the contexts of high and low maternal aggression, respectively. In a sample of adolescents of Mexican-origin, Schriber et al. (2017) found that the adverse and protective effects of community violence and family connectedness, respectively, on depressive symptoms were magnified in youth with larger hippocampal volume. In a recent study of newborn infants, Overfeld et al. (2020) found that postnatal enrichment was positively associated with early cognitive development only in infants with larger hippocampal volume. Across these studies, individuals with smaller hippocampal volume appear to be less sensitive to both the costs and the benefits associated with environmental support and adversity (Overfeld et al., 2020; Schriber et al., 2017; Whittle et al., 2011). It is possible, therefore, that larger hippocampal volume is associated with increased sensitivity to environmental context.

The hippocampus is involved in regulating psychological and biological processes such as stress, learning, memory, and cortisol response (Bangasser & Shors, 2007; Østby et al., 2012; Pruessner et al., 2007) that may both confer sensitivity to physical environments and contribute to cellular aging. For example, larger hippocampal volume may support stronger consolidation and representation of events and contexts (Østby et al., 2012), which may increase the salience of environmental cues related to the presence versus absence of pollution. Moreover, larger hippocampal volume has been associated with heightened cortisol reactivity (Pruessner et al., 2007), which has been posited to play a role in filtering and encoding environmental information (Del Giudice et al., 2011) and in accelerating telomere shortening (Jiang et al., 2019). To date, however, studies have not considered whether larger hippocampal volume indexes sensitivity or vulnerability to the adverse effects of polluted environments.

In previous studies, researchers have identified larger hippocampal volume as a potential neurobiological marker of increased sensitivity to a *social* context (Overfeld et al., 2020; Schriber et al., 2017; Whittle et al., 2011). In the current investigation, we explored whether these findings extend to sensitivity to a *physical* context. Specifically, we evaluated whether hippocampal volume moderates the association between neighborhood-level pollution burden and telomere length in a manner consistent with the biological sensitivity to

context or diathesis stress model. Consistent with findings of previous studies of neurobiological sensitivity to social context, the association between pollution burden and shorter telomere length may be stronger for youth with larger hippocampal volume; these youth may have the longest and shortest telomere length values in the context of low and high pollution burden, respectively. Conversely, youth with smaller hippocampal volume may be buffered from the association between pollution burden and telomere length.

2 | METHODS

2.1 | Participants and procedure

Participants were adolescents from the San Francisco Bay Area who are part of an ongoing, longitudinal study of early life stress and neurodevelopment during puberty (King et al., 2019; Miller et al., 2020, 2021). 214 adolescents participated at baseline (Time 1) (121 females; mean age at baseline = 11.40, SD = 1.0; 10.3% Asian American, 20.1% biracial, 8.4% Black, 8.4% Hispanic/Latinx, 6.5% Other, 44.4% White, 1.9% did not report; median family income = $100K–$125K, range ≤ $5K –≥ $150K). In addition, 156 adolescents provided useable data for the current analysis at a follow-up assessment approximately two years later (Time 2). As reported previously (King et al., 2019; Miller et al., 2020, 2021), exclusion criteria for this study included an inability to undergo magnetic resonance imaging (MRI), a history of neurological disorder or major medical illness, cognitive, or physical challenges that could interfere with study procedures, nonfluent English speakers, and, for female participants, the onset of menses. Male and female participants were matched on self-reported pubertal stage at the baseline assessment; thus, on average, males were older than females in our sample (mean difference = 0.74 years, $t(212) = 5.48$, $p < 0.001$).

2.2 | Pollution burden

Pollution burden at the census tract level was based on data provided by the California Environmental Protection Agency (EPA; CalEnviroScreen 3.0; OEHHA, 2017). Pollution burden scores are based on up to 12 indicators of pollution exposures and environmental effects (i.e., adverse environmental conditions related to pollution). Exposure indicators are ozone concentrations, fine particulate matter concentrations, diesel particulate matter emissions, drinking water contaminants, pesticide use, toxic releases from facilities, and traffic density. Environmental effect indicators are cleanup sites, groundwater threats, hazardous waste, impaired water bodies, and solid waste sites and facilities. Percentile scores for each indicator, representing levels relative to other census tracts in California, were averaged to create exposure and environmental effect scores. Pollution burden scores as calculated by the California EPA were computed as the average of exposure and half-weighted environmental effect scores (OEHHA, 2017).

2.3 | MRI image acquisition and processing for hippocampal volume measurement

As described previously (Humphreys et al., 2019; Miller, Dennis, et al., 2021), at Time 1 and Time 2 participants completed a T1-weighted MRI scan on a 3T GE Discovery MR750 (GE Medical Systems, Milwaukee, WI, USA) at the Stanford Center for Cognitive

and Neurobiological Imaging. T1-weighted images were collected using a spoiled echo gradient pulse sequence that lasted 5.15 min and consisted of 186 sagittal slices, TR/TE/TI = 6.24/2.34/450 ms, flip angle = 12°, and voxel size = 0.9 mm × 0.9 mm × 0.9 mm.

All T1-weighted images were visually inspected for motion artifact (e.g., ringing artifacts) prior to segmentation and volume extraction from FreeSurfer. As detailed in (Humphreys et al., 2019; King et al., 2019), we used the "recon-all" pipeline of FreeSurfer version 5.3 to perform tissue segmentation and to estimate hippocampal volume from T1-weighted structural images (Fischl et al., 2002). All hippocampal segmentations were visually inspected against the T1-weighted image for accuracy by three trained technicians. We converted hippocampal volumes for each hemisphere into z-scores. Volumes with z-scores that were greater than 2.5 or less than −2.5 were visually inspected again for accuracy. Segmented hippocampal volumes that did not pass any of these steps were excluded from analyses. We excluded 16 and 4 left and right hippocampal volume values, respectively, at Time 1. We excluded 17 and 1 left and right hippocampal volume values, respectively, at Time 2. We computed bilateral hippocampal volume as the average of left and right hippocampal volume. If a participant provided useable hippocampal volume for only one hemisphere, then that value was included in the analysis. In total, we had hippocampal volume data for 184 participants at Time 1 and 132 participants at Time 2.

2.4 | Telomere length

These telomere length data were presented for different purposes in Humphreys et al. (2020) and Miller et al. (2020). Briefly, and as described previously, genomic DNA was purified from 500 μl of saliva in the Oragene DNA Kit (DNA Genotek, Kanata, ON, Canada) with the DNA Agencourt DNAdvance Kit (cat. No. A48705; Beckman Coulter Genomics, Brea, CA, USA). DNA was quantified by Quant-iT PicoGreen dsDNA Assay Kit (cat. No. P7589; Life Technologies, Grand Island, NY, USA) and run on 0.8% agarose gels to check the integrity. DNA samples were stored at −80°C. Telomere length measurement was adapted from the method originally published by Cawthon (2002) (see the Supplement for further details regarding parameters for assaying telomere length). Telomere length data were available for 212 and 121 participants at Time 1 and Time 2, respectively.

2.5 | Statistical analyses

We conducted regression analyses to examine whether hippocampal volume moderated the association between pollution burden and telomere length at Times 1 and 2. Predictors within the Times 1 and 2 models included participant age at saliva sample collection, sex, intracranial volume (ICV), neighborhood poverty, pollution burden, hippocampal volume, and the interaction between pollution burden and hippocampal volume. Neighborhood poverty was assessed using data indicating the percentage of residents within a given census tract with income less than two times the federal poverty level. The California EPA converted these rates into percentiles representing poverty relative to other census tracts in California. Sex was recoded such that male and female were −0.5 and 0.5, respectively (see Kraemer & Blasey, 2004 for details about this centering strategy). All other predictor variables were standardized prior to forming interaction terms. A statistically significant interaction effect indicates that the relation between pollution burden and telomere length varies meaningfully at different levels of hippocampal volume. To determine the form of a statistically significant interaction effect, we conducted follow-up analyses using

simple slope tests at 1 SD above and below the mean of hippocampal volume (see Aiken & West, 1991 for details about simple slopes analysis). That is, we examined the associations between pollution burden and telomere length at specific values of hippocampal volume that we defined as representing large and small volumes. Prior to conducting regression analyses, we used boxplots to inspect variables for extreme outliers. We defined extremely high outliers as values more than three times the interquartile range (i.e., quartile 3 minus quartile 1, representing the spread of the middle 50% of the data for a given variable) above the third quartile. We defined extremely low outliers as values less than three times the interquartile range below the first quartile. This led us to winsorize one high telomere length value at Time 2 to the next most extreme value (Erceg-Hurn & Mirosevich, 2008). We have used these methods to detect and winsorize outliers in prior studies (Miller et al., 2019; Miller, Dennis, et al., 2021). We conducted two sets of models for each analysis – one that primarily controlled for additive effects of covariates, and one that additionally controlled for covariates as confounding variables by including interactions between each covariate and hippocampal volume and each covariate and pollution burden (Keller, 2014). To account for missing data, all analyses were conducted using the lavaan package in R (Rosseel, 2012) and model parameters were generated using full information maximum likelihood estimation (Kline, 2011).

We used three approaches to evaluate whether an interaction effect was more consistent with the biological sensitivity to context model or the diathesis stress model. First, we visually inspected interaction plots for the presence of a crossover effect, which conforms more to biological sensitivity to context. Second, we applied a proportion-affected index to quantify the number of participants who are differentially affected by the moderator (Roisman et al., 2012). This measure indicates the percentage of participants who show shorter telomere length in the context of high pollution burden and the percentage of participants who show longer telomere length in the context of low pollution burden. We interpreted proportions closer to 0.50 as evidence in favor of the biological sensitivity to context model because the effect is roughly equally represented at both low and high pollution burden. We interpreted proportions closer to 1 as evidence in favor of the diathesis stress model because the effect is primarily represented at high, but not at low, pollution burden. Although there are not well-established thresholds for determining whether proportion-affected index values firmly support one theoretical model over another, Roisman et al. (2012) suggested using 0.84 as a default cutoff for starting to question whether results conform more strongly with the diathesis stress than with the biological sensitivity to context model. In our analysis, a proportion-affected index above 0.84 indicates that fewer than 16% of the participants in our sample experience longer telomere length in the context of low pollution burden; this would not provide strong evidence for the biological sensitivity to context model, which posits that sensitive individuals fare better than others in more positive or supportive environments (Boyce, 2016). Our third approach to evaluate interaction effects was to test simple slopes of hippocampal volume predicting telomere length at high and low levels of pollution burden. We interpreted differential significant associations between hippocampal volume and telomere length at high and low levels of pollution burden as further evidence in favor of the biological sensitivity to context model.

3 | RESULTS

Descriptive statistics and presented in Table 1. Pearson correlations are presented in Table 2. Based on Pearson correlations, measures of telomere length and hippocampal volume had high rank-order stability from Times 1 to 2. Older adolescents and male

TABLE 1 Descriptive statistics

	Mean or % (SD)	Range
Sex (female)	**57%**	**male/female**
T1 age	11.38 (1.04)	9.17 – 13.98
T2 age	13.35 (1.05)	11.15 – 15.85
T1 telomere	1.50 (0.25)	0.81 – 2.14
T2 telomere	1.39 (0.23)	0.93 – 2.04
T1 ICV	8.3%	
T2 ICV	9.2%	
T1 Hippocampal volume	4249.41 (430.18)	3418.35 – 5415.50
T2 Hippocampal volume	4385.27 (430.31)	3317.90 – 5599.85
Neighborhood poverty	24.53% (21.34)	0 – 99
Pollution Burden	32.72% (23.11)	0 – 100

Note. T1 = Time 1; T2 = Time 2; ICV = intracranial volume. Neighborhood poverty and pollution burden are presented in percentiles for a given census tract relative to other census tracts in California.

participants had larger hippocampal volume than did younger adolescents and female participants at Times 1 and 2. Neighborhoods with greater pollution burden also had higher rates of poverty. Telomere lengths from either time point were not significantly correlated with hippocampal volume, pollution burden, or neighborhood poverty. Telomere length was shorter ($t(119) = 6.14$, $p < 0.001$), and hippocampal volume was larger ($t(124) = 6.53$, $p < 0.001$), at Time 2 than at Time 1.

The cross-sectional regression models for Times 1 and 2, controlling for additive covariate effects, are presented in Table 3. Here in the text, we present the statistics for models that control for both additive and confounding covariate effects (Keller, 2014). In the regression model for Time 1, the interaction of pollution burden and hippocampal volume significantly predicted telomere length ($\beta = -0.20$, SE = 0.10, 95% CI[–0.39, –0.02], $p = 0.034$). Figure 1 presents the simple slopes of the interaction effect. At average levels of hippocampal volume, pollution burden was negatively associated with telomere length ($\beta = -0.19$, SE = 0.07, 95% CI[–0.33, –0.04], $p = 0.012$); this association was magnified in participants with larger hippocampal volume ($\beta = -0.40$, SE = 0.13, 95% CI[–0.65, –0.15], $p = 0.002$). In contrast, in participants with smaller hippocampal volume, the association between pollution burden and telomere length was weaker and not statistically significant ($\beta = 0.02$, SE = 0.12, 95% CI[–0.21, 0.26], $p = 0.844$). Covariates in the model (sex, age, ICV, and neighborhood poverty), and interaction between covariates and hippocampal volume and pollution burden, were not associated with telomere length at Time 1 (all ps > 0.104). Analyses that considered either left or right hippocampal volume yielded similar findings to our primary model, although the interaction of left hippocampal volume with pollution burden was not statistically significant (ps = 0.091 or 0.050 in models controlling for additive covariate effects or additive and confounding covariate effects, respectively). These analyses are presented in the Supplement (Supporting Information).

The crossover point of the interaction effect was at a value of approximately 46 for pollution burden score; 25% of the sample lived in communities with a higher pollution burden score than this value. This proportion-affected index value is below our 0.84 proportion cutoff, and therefore, is more consistent with the biological sensitivity to context than with the diathesis stress model (Roisman et al., 2012). To further evaluate the interaction effect, we tested whether hippocampal volume was differentially associated with telomere length at low and high levels of pollution burden by treating pollution burden as the

TABLE 2 Pearson correlations

	1	2	3	4	5	6	7	8	9	10	11
1. Sex (female = 1)	1										
2. T1 sample age	–0.35***	1									
3. T2 sample age	–0.32***	0.95***	1								
4. T1 telomere	0.10	–0.13	–0.16	1							
5. T2 telomere	0.09	–0.14	–0.14	0.68***	1						
6. T1 ICV	–0.30***	0.17*	0.10	0.00	0.12	1					
7. T2 ICV	–0.37***	0.36***	0.39***	0.04	–0.02	0.48***	1				
8. T1 hippocampal volume	–0.29***	0.24***	0.23*	0.05	0.13	0.49***	0.46***	1			
9. T2 hippocampal volume	–0.31***	0.26**	0.28**	0.06	0.11	0.35***	0.50***	0.90***	1		
10. Neighborhood poverty	–0.08	–0.17*	–0.12	0.05	0.11	0.09	–0.07	0.04	–0.03	1	
11. Pollution burden	–0.00	–0.09	–0.06	–0.12	0.09	0.01	–0.03	–0.05	–0.12	0.35***	1

Note. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$. T1 = Time 1; T2 = Time 2. Neighborhood poverty and pollution burden are presented in percentiles for a given census tract relative to other census tracts in California.

TABLE 3 Cross-sectional regression models at Times 1 and 2

	β	SE	95% CI	p
Outcome: T1 Telomere Length				
Sex	0.11	0.08	−04, 0.25	0.149
Age	–0.12	0.07	–0.26, 0.02	0.104
ICV	0.02	0.08	–0.15, 0.19	0.818
Neighborhood poverty	0.09	0.08	–0.06, 0.24	0.223
Pollution burden	–0.19	0.07	–0.34, –0.05	0.008**
Hippocampal volume	0.08	0.08	–0.09, 0.25	0.344
Pollution burden × Hippocampal volume	–0.16	0.07	–0.31, –0.02	0.030*
Outcome: T2 Telomere Length				
Sex	0.13	0.10	–0.07, 0.33	0.202
Age	–0.17	0.10	–0.37, 0.04	0.107
ICV	0.05	0.13	–0.19, 0.30	0.667
Neighborhood poverty	0.08	0.10	–0.12, 0.28	0.440
Pollution burden	0.02	0.11	–0.20, 0.24	0.829
Hippocampal volume	0.23	0.11	0.01, 0.45	0.045*
Pollution burden × Hippocampal volume	–0.10	0.11	–0.32, 0.12	0.364

Note. *$p < 0.05$, **$p < 0.01$. These models control for the additive effects of covariates. Results for models controlling for both additive and confounding effects of covariates are presented in the text.

moderator variable. In communities characterized by *less* pollution burden, greater hippocampal volume was associated with longer telomere length at Time 1 ($\beta = 0.27$, SE = 0.13, 95% CI[0.01, 0.53], $p = 0.041$). In communities characterized by *greater* pollution burden, however, the negative association between hippocampal volume and telomere length was not statistically significant ($\beta = –0.15$, SE = 0.13, 95% CI[–0.41, 0.11], $p = 0.250$).

We conducted a series of models to test whether there was a similar interaction effect at Time 2. The association between pollution burden and telomere length at Time 2 was not moderated by hippocampal volume at Time 1 or Time 2 (both ps > 0.294). These interaction effects were also not statistically significant in a model controlling for Time 1 telomere length (both ps > 0.522). Controlling for age, sex, and poverty, hippocampal volume at Time 2 was positively associated with telomere length at Time 2 ($\beta = 0.18$, SE = 0.08, 95% CI[0.02, 0.34], $p = .024$) over and above the effect of Time 1 telomere length ($\beta = 0.68$, SE = 0.05, 95% CI[0.59, 0.78], $p < 0.001$).

We conducted a path analysis as a third type of model to evaluate whether, for youth with larger hippocampal volume, pollution burden is indirectly associated with Time 2 telomere length via Time 1 telomere length (see Figure 2). We computed the indirect effect as the product of the standardized beta coefficient linking pollution burden to telomere length at Time 1, and the standardized beta coefficient linking telomere length at Time 1 to telomere length at Time 2. We used the product of these beta coefficients at high levels of hippocampal volume, and used the Sobel test to test the statistical significance of the indirect effect (Sobel, 1982). In youth with larger hippocampal volume at Time 1, greater pollution burden was indirectly associated with shorter telomere length at Time 2 through shorter telomere length at Time 1 (indirect $\beta = –0.25$, SE = 0.08, 95% CI[–0.40, 0.10], $p = 0.002$).

Additional analyses examining a three-way interaction effect involving age, pollution burden, and hippocampal volume, interaction effects of hippocampal volume with

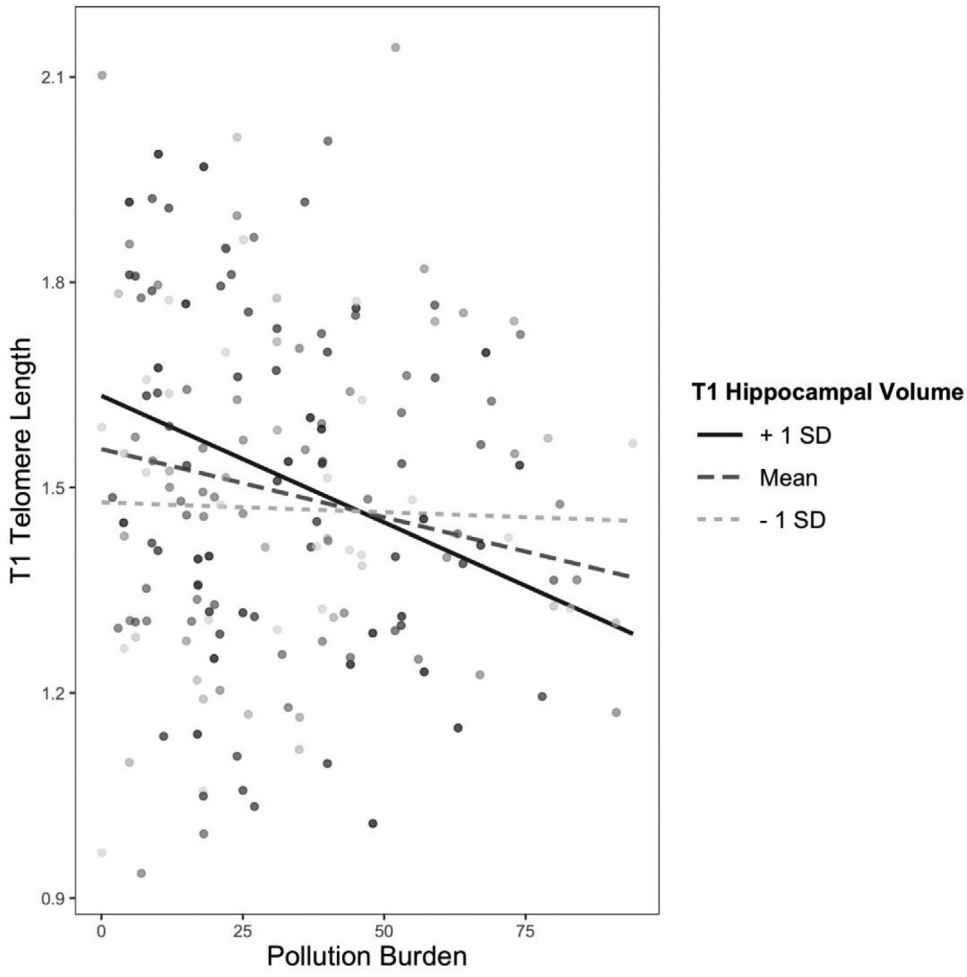

FIGURE 1 Hippocampal volume moderates the association between pollution burden and telomere length at Time 1. *Note*. The data points in the plot follow a color gradient. Smaller hippocampal volume values are presented as lighter in color and larger hippocampal volume values are presented as darker in color

specific pollution burden indicators, as well as plots of the distributions of pollution burden and pollution burden indicators, and plots of the correlations among pollution indicators, are presented in the Supplement.

4 | DISCUSSION

Children and adolescents growing up in areas with higher levels of environmental pollution and contaminants may be at risk for experiencing accelerated biological aging. Indeed, exposure to air pollution and heavy metals has been associated with shorter telomere length in pediatric samples (Fillman et al., 2016; Lee et al., 2019). However, it is likely that some youth are more sensitive than others to the adverse effects of pollution (Trentacosta & Mulligan, 2020). We tested whether hippocampal volume moderated the association between neighborhood-level pollution burden and telomere length in a sample of adolescents living in the San Francisco Bay Area. We found that hippocampal volume interacted

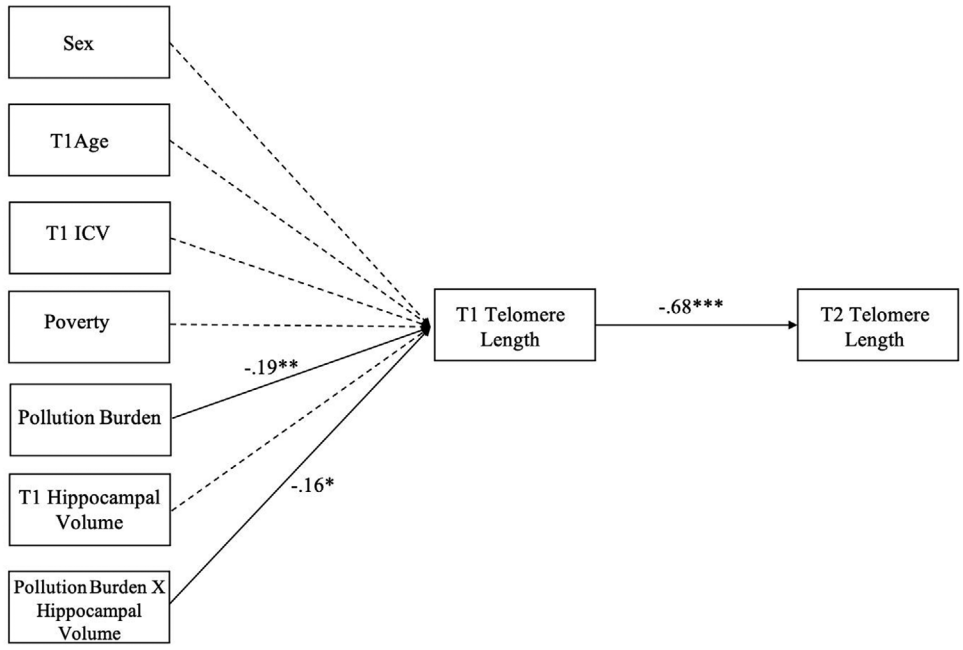

FIGURE 2 Path analysis model testing whether pollution burden is indirectly associated with Time 2 telomere length via Time 1 telomere length for adolescents with larger hippocampal volume. *Note.* $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

with pollution burden in a manner consistent with the biological sensitivity to context model (Belsky, 2016; Boyce, 2016). Specifically, at average levels of hippocampal volume, greater pollution burden was associated with shorter telomere length at our baseline assessment. This negative association was magnified in adolescents with larger hippocampal volume. In contrast, there was no association between pollution burden and telomere length in adolescents with smaller hippocampal volume. This interaction effect was not present at the follow-up assessment conducted approximately two years later. However, for youth with larger hippocampal volume, pollution burden was indirectly associated with telomere length later in adolescence through telomere length in early adolescence.

Our findings are consistent with prior research suggesting that hippocampal volume is a neurobiological marker of susceptibility to social contexts (Schriber et al., 2017; Whittle et al., 2011). In the current investigation we extended this work to consideration of a physical context – pollution burden. Visually, the interaction effect of hippocampal volume and pollution burden on telomere length appeared to be disordinal, which is more consistent with the biological sensitivity to context model than with the diathesis stress model (Widaman et al., 2012). Our proportion-affected index also indicated that the interaction effect was consistent with the biological sensitivity to context model (Roisman et al., 2012). However, in contrast, and contrary to what the biological sensitivity to context model would predict, we did not find statistically significant associations between hippocampal volume and telomere length at *both* low and high levels of pollution burden; hippocampal volume was significantly (positively) associated with telomere length only under low pollution burden conditions, whereas the negative association between hippocampal volume and telomere length under high pollution conditions was not statistically significant. It is possible that more power is needed to clarify the inconsistency that we observed between this finding and the proportion-affected index, or that higher levels of pollution burden are

necessary to observe the negative association between hippocampal volume and telomere length.

Adolescents with larger hippocampal volume may be more attuned to cues of environmental pollution, or may be more affected by exposure to pollution. In contrast, smaller hippocampal volume may reflect or contribute to resilience in adolescents to the adverse effects of pollution burden on cellular aging. One potential explanation for these findings is that hippocampal volume tracks with psychological and biological processes that increase openness to environmental input and that are involved in regulation of cellular aging. Larger hippocampal volume may be related to a greater capacity for processes involved in memory and learning, leading to stronger binding and representation of contextual cues over time (Ergorul & Eichenbaum, 2004; Østby et al., 2012). Thus, one interpretation of our findings is that adolescents with larger hippocampal volume process environmental input related to the presence or absence of pollution burden more deeply and over longer periods of time.

Hippocampal volume has also been implicated in stress biology, including increased production of cortisol in response to challenge (Pruessner et al., 2007). Increased neurobiological responsivity to challenge in the hypothalamic pituitary adrenal axis (HPA-axis), as well as other stress biology systems, may support encoding and filtering processes that increase openness to environmental input (Del Giudice et al., 2011). Most of the studies in this area have considered biological sensitivity to social stressors; it is important to note, however, that specific types of pollution, such as fine particulate air pollution, have been linked to increased reactivity in stress biology systems (Miller et al., 2020; Miller et al., 2019). In the context of heightened pollution burden, larger hippocampal volume may be involved in repeated or chronic activation of stress biology systems that, in turn, accelerates telomere erosion (Jiang et al., 2019). Conversely, larger hippocampal volume may be related to processes that increase sensitivity to benefits that can be derived from more advantaged and less polluted contexts, some of which may contribute to slower cellular aging. In combination with results of prior studies (e.g., Overfeld et al., 2020; Schriber et al., 2017; Whittle et al., 2011), our findings point to the possibility that hippocampal volume indexes whether individuals are more or less biologically reactive, and thus more open, to both social and physical environmental input.

It is important to place this interpretation of our findings in the context of prior research suggesting that exposure to early life stress is associated with reduced hippocampal volume (Hanson et al., 2015; Humphreys et al., 2019). The hippocampus is rich in glucocorticoid receptors (Jacobson & Sapolsky, 1991), and exposure to glucocorticoids as a result of stress can disrupt neurogenesis and synaptogenesis processes, ultimately leading to alterations in hippocampal volume. If early life stress is associated with smaller hippocampal volume, why would this neurophenotype, in our study and in prior studies (Deane et al., 2020; Schriber et al., 2017), appear to limit or mitigate adverse environmental effects? One potential consequence of altered neurobiology following early life stress is reduced plasticity (Callaghan & Tottenham, 2016) or reduced openness to environmental influence (Del Giudice et al., 2011). In this context, it is possible that while some neural alterations following early life stress serve as pathways that increase risk for health problems, they may also help to limit adolescents' sensitivity to subsequent negative experiences (Miller et al., 2022). From this perspective, relative insensitivity to environmental influence related to reduced hippocampal volume may be a developmental adaptation to early life stress that helps to limit both vulnerability and openness to subsequent negative and positive experiences (Miller et al., 2022). In our study, youth with smaller hippocampal volume appeared to be less vulnerable to the adverse effects of high pollution burden on telomere length, but also did not have longer telomere length in the context of low pollution burden. We believe

that these findings, combined with prior work on early life stress, fit with a developmental adaptation framework.

In accord with prior studies of adolescents, telomere length decreased and hippocampal volume increased from Time 1 to Time 2 (Coupé et al., 2017; Humphreys et al., 2016; Wierenga et al., 2014). In addition, individual differences in telomere length and hippocampal volume were highly stable over time. However, the interactive effect of hippocampal volume and pollution burden on telomere length was not present at the follow-up assessment. In addition, the interaction effect did not prospectively predict the development of telomere length at Time 2. The presence of a statistically significant interaction effect at Time 1 but not at Time 2 may be due to the relatively lower rank-order stability of telomere length, compared to hippocampal volume, over time. A larger sample may be necessary to detect a statistically significant interaction effect at Time 2. Nevertheless, for adolescents with larger hippocampal volume, there was an indirect effect of pollution burden on telomere length at Time 2 through telomere length at Time 1. Thus, for adolescents with larger hippocampal volume, pollution burden may be particularly relevant to cellular aging processes early in adolescence rather than being directly involved in changes in telomere length over the course of adolescence. Nevertheless, for these adolescents, the effect of high or low pollution burden on telomere length in early adolescence may predispose them to develop shorter or longer telomere length, respectively, later in adolescence. It is possible that the association between pollution exposure and telomere length, and individual differences in susceptibility, are present prior to adolescence. For example, recent work suggests that maternal prenatal exposure to higher levels of air pollution is associated with shorter newborn telomere length, particularly in males (Song et al., 2019). Interestingly, larger hippocampal volume in infancy has been found to reflect increased sensitivity to environmental enrichment (Overfeld et al., 2020). In the future, researchers should test the possibility that hippocampal volume moderates the links between pollution and cellular aging metrics in infancy and childhood.

We should note that previous research on environmental effects and telomere length has focused primarily on specific pollutants (Fillman et al., 2016; Lee et al., 2019); in contrast, we focused on a broader measure of pollution burden that is based on multiple census tract indices of pollutant levels and adverse environmental effects related to pollution. We found that interaction effects were largely not present for specific indicators of pollution burden, potentially due in part to the distributions of these variables (see Supplement). Conversely, overall pollution burden may reflect an important feature of the environment for some adolescents. Specifically, the cumulative risks and adversities related to the degree of community pollution burden may heighten risk for shorter telomere length, and hippocampal volume may indicate processes that buffer or exacerbate pollution burden-related effects. Recent research has demonstrated the importance of neurobiological measures in buffering against or exacerbating against the negative effects of other community-level factors, such as neighborhood violence, on adolescent health (Miller et al., 2018). The present study extends this work by providing evidence that hippocampal volume moderates risk for accelerated cellular aging in adolescents who live in more polluted communities.

We should note five limitations of this study. First, the current analyses were not part of the original aims of our longitudinal study. Consequently, we did not have complete residential address histories for participants and, therefore, cannot estimate cumulative pollution burden. It is likely, however, that even if they move, individuals grow up in similar communities over the course of childhood and adolescence, and thus experience relatively stable levels of pollution burden. Nevertheless, it will be important for future longitudinal research examining biological sensitivity to physical contexts to consider timing and

duration effects of pollution. Indeed, our findings suggest that hippocampal volume moderates how pollution burden is associated with telomere length in earlier adolescence, but that this interaction effect does not directly predict telomere length later in adolescence. Second, our measure of pollution burden is not a measure of personal exposure, and does not elucidate the specific pollutants or adverse environmental conditions that are implicated most strongly in telomere length. Studies that consider biomarkers of exposure (Trentacosta & Mulligan, 2020) and personal monitoring of pollutant levels across multiple environments (Gulliver & Briggs, 2004) will be important for more accurately estimating exposures and identifying specific environmental mechanisms of variability in telomere length. Third, our findings do not provide causal evidence for the link between greater pollution burden and shorter telomere length. It is possible that hippocampal volume regulates sensitivity to unmeasured environmental features that co-occur with overall pollution, such as noise pollution or traffic. As a related point, our findings do not speak to whether a specific type of pollution is particularly relevant to telomere shortening. Future research should consider whether changes in pollution burden, or changes in exposure to specific types of pollutants, may affect cellular aging metrics differently for youth with larger versus smaller hippocampal volume. Fourth, we examined high versus low neighborhood pollution burden, similar to prior studies of biological sensitivity to context that considered high versus low levels of social adversity (Miller, Chahal, et al., 2021; Obradović et al., 2011; Obradović et al., 2010). Low levels of pollution burden may not necessarily imply the presence of positive, enriching physical contexts (e.g., safe green and blue spaces). It will be important to consider positive features and resources of neighborhoods to test more comprehensively biological sensitivity to physical contexts. Finally, we used telomere length during adolescence as our outcome measure. There is debate regarding which health outcomes are linked specifically to shorter telomere length (Smith et al., 2019); therefore, beyond a consideration of cellular aging processes in adolescence, the implications of our findings for short- and long-term health are less clear.

Despite these limitations, the current study provides novel evidence that hippocampal volume moderates the association between neighborhood pollution burden and telomere length in early adolescence. Adolescents with larger hippocampal volume had both the longest and the shortest telomere length at our baseline assessment in the context of low and high pollution burden, respectively. In contrast, adolescents with smaller hippocampal volume were buffered from the link between pollution burden and telomere length. This work extends the biological sensitivity context model to include a consideration of individual differences in risk and resilience to the harmful effects of pollution on health. Further, for youth with larger hippocampal volume, pollution burden was indirectly associated with telomere length 2 years later through its association with telomere length in early adolescence. Thus, for some adolescents, living in more or less polluted communities may predispose them to experience faster or slower cellular aging processes that are stable during adolescence.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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